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A REVIEW ON HPMC CAPSULE

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ABSTRACT

The main cause of gelatin capsule instability is the deleterious effects of temperature and relative humidity fluctuations, on the mechanical integrity of the capsule shells, which can also have a severe impact on the fill material. Additionally, the selection of fill materials is severely constrained by their unique chemical makeup, physical characteristics, or hygroscopicity. The hunt for a superior substitute capsule shell material has been motivated by additional reports of unpredictably disintegrating and dissolving hard gelatin capsules in experimental investigations. The current review intends to give an overview of the Hydroxyl Propyl Methyl Cellulose (HPMC) as a capsule shell material whose physicochemical, pharmaceutical biopharmaceutical properties, *in vitro/ in vivo* performance, storage and stability are superior to gelatin capsules. The HPMC capsule widens the options for choosing various types of fill materials and offers a highly adaptable and widely accepted platform that can address many issues now plaguing the pharmaceutical and nutraceutical sectors. A new section on the impact of several conditions on the *in vitro* dissolution studies of HPMC capsules is introduced in the present topic. There are no adverse effects in *in vitro/in vivo* studies of HPMC capsules in aqueous medium. However, improvements in the manufacturing and filling of HPMC capsule shells as well as thorough research on the impacts of many parameters on their *in vitro/in vivo* studies is desired to establish their superiority over hard gelatin capsules in future.

Key works: Gelatin capsule shell, Problems associated with Gelatin, Hydroxy Propyl Methyl Cellulose (HPMC) as capsule shell and its advantages

I. INTRODUCTION [1, 2]

The capsule is a flexible unit solid dosage form for oral administration that is intended to enclose an active pharmaceutical ingredient (API) and acceptable excipients in either a hard gelatin shell or a soft gelatin shell. Due to the characteristics of the shell, capsules are able to preserve the encapsulated medicine from deterioration brought on by ambient oxygen, light, moisture, etc. Due to its non-toxicity, solubility in biological fluids at body temperature, ability to undergo heat gelation, and ability to create a robust, flexible, and homogenous film, gelatin is the most commonly used capsule shell material. Gelatin is frequently utilized to create innovative drug delivery devices, such as wafers, and to stabilize pharmaceutical solutions. However, gelatin capsules have some issues viz. Cross linking, Problem with stability and moisture content Dissolution and disintegration in relation to temperature and some issues in religious aspects. Because of these inherent gelatin features that contribute to impaired *in vitro* stability of gelatin capsules. The following list includes issues with gelatin selection and performance

a) Problem with Cross linking [3]

Gelatin is a protein that occurs naturally which can be hydrolyzed to produce amino acids which may react with molecules particularly aldehydes or any formulation component that has an aldehydic functional group/ reducing sugars/, metal ions/ plasticizers/ preservatives. Gelatin is incompatible with surfactants as well as anionic and cationic polymeric excipients **[2]**. Excipients such lipids, polyethylene glycol and its ethers, aliphatic alcohols or phenols, polysorbates, and esters of unsaturated fatty acids are frequently utilized in the creation of various dosage forms and can undergo auto-oxidation to produce aldehydes. The aldehydic end-products of degradation may interact with gelatin through cross-linking, forming an excipient- excipient/ drug interaction which may lead to. delayed disintegration and dissolution of gelatin shell. Environmental factors such as high humidity, high temperature and UV light can also induce cross-linking reactions

b) Problem with stability and moisture content [3, 4]

Gelatin contains water that works as a plasticizer and creates a stiff but flexible film (13%w/w to 16%w/w). Changes in the environment's relative humidity can result in either brittle or wet shells, which can occasionally have a negative effect on the fill material. The main area of concern for the use of capsules in overly humid/dry settings is the sensitivity of gelatin to extremes of humidity.

c) Problem with Dissolution and disintegration in relation to temperature [5]

When examining how well capsules dissolve and disintegrate, temperature is an important factor that needs to be considered. Since gelatin's solubility reduces as temperature drops below 37 °C, a problem occurs. The capsule shells are insoluble below 30 °C and simply absorb water, expand, and distort. As a result, 37 °C ±1 °C has been established as the upper limit by compendia and pharmacopoeia of many nations.

d) A religious viewpoint [6]

Some segments of the public, including vegetarians, vegans, and members of certain ethnic or religious groups who follow diets that ban the consumption of animal products, are concerned about the animal source of gelatin.

e) Unique manufacturing circumstances [7]

Hard gelatin capsules cannot be filled with liquid or semi-solid substances. Although soft gelatin capsules offer a superior substitute for these fill materials, their production calls for certain manufacturing procedures and strict environmental temperature and humidity control. The air's temperature and humidity are held constant during the encapsulation process at 57–59 °F and 20% RH. Drying must be done at a setting that is equivalent to 25 °F. For the production of soft capsules, typical environmental parameters are 68 °F and 20% RH or 78 °F and 15% RH. Gelatin's afore mentioned drawbacks and problems as a capsule shell have sparked the development of other materials. A thorough examination of the literature turns up a few studies on HPMC-based capsule shells and names of companies that sell empty HPMC capsule shells on the global market. To yet, no single study has been able to shed light on the different criteria that HPMC as a substitute for gelatin in capsule shells satisfies. Studies on the compatibility of HPMC with different excipients and fill materials, as well as information on the impact of various parameters on the dissolution of empty and filled HPMC capsules, are lacking despite the fact that indications about the in vitro and in vivo performance of HPMC capsules have been found. The purpose of the current review is to fill up these gaps in our thorough understanding of HPMC as a capsule shell material. Because of above mentioned problems there is a need for a superior replacement for capsule shell material.

II. AN ALTERNATE CAPSULE SHELL MATERIAL IS HPMC [8, 9, 10]

The alternative capsule shell material should preferably be derived from plants, avoid cross-linking reactions with various excipients, be stable during production and storage to changes in environmental temperature and humidity, not show temperature-dependent disintegration or dissolution, and be able to hold any fill material. A capsule with gelatin-like behavior that can be used with existing filling machinery is required for commercial-scale manufacture. A polymer for capsules with a track record of safety and widespread regulatory acceptability will be accepted by regulatory agencies. Clinicians request a substitute whose therapeutic efficacy is comparable to that of gelatin and whose patient compliance is guaranteed. Hypromellose, commonly known as Hydroxy Propyl Methyl Cellulose (HPMC). It is a cellulose-based polymer (derived from plant sources) that has been used in pharmaceutical products for many years as an excipient in various formulations and coating applications, effectively addresses the majority of the drawbacks of gelatin.

According to US Code of Federal Regulations Title 21 Section 172.874 and EU Regulation (EC) No. 1333/2008, HPMC is allowed as an addition for human consumption and meets with international pharmaceutical regulatory standards. Additionally, the US FDA Inactive Ingredient Database lists it. In line with 21 CFR 172.874 and Regulation (EC) No 1333/2008, HPMC is approved as a food additive for human consumption and complies with USP/NF, EP, and JP requirements. It is generally acknowledged as a non-toxic and non-irritating substance and is listed in the US FDA Inactive Ingredients Database. Since it is produced in facilities that are ISO 9001 certified and in accordance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical excipients, it is widely accessible and acceptable.

HPMC can be used as a substitute for gelatin as a construction material for capsule shells. HPMC has a number of physicochemical and pharmaceutical advantages, including the following:

a. It is semi-synthetic in nature and derived from plant cellulose
b. There is no cross-linking issue with the excipients because the polymer is free of amino acids
c. Suitable for a range of fill materials that contain an aldehydic group
d. Due to the reversible thermal gelation feature, it quickly dissolves in cold water and produces a colloidal solution.
e. It forms a flexible film with precise dimensions.
f. Water does not act as a plasticizer for HPMC in comparison to gelatin. Hence it is more stable under a variety of temperature and moisture conditions.

g. They are stable at low humidity levels during storage or when filled with hygroscopic formulations.
h. They won't become brittle when dried to 1% moisture content.
i. Water has been seen to diffuse through HPMC capsule films at a rate that is roughly half that of gelatin capsules. This suggests that HPMC capsules are more suited for items that need to be moisture-resistant.
j. HPMC capsules are more stable at moisture levels of 3-5% and are resistant to breaking during processing and transit. Due to its non-ionic nature, it is compatible with the majority of regularly used excipients and APIs.
k. Adhesion property and shell texture of HPMC film facilitates application of modified release uniform coating with excellent performance characteristics,
l. HPMC capsules does not require TSE (Transmissible Spongiform Encephalopathy) certification, which reduces the time required for documentation and regulatory filings,
m. HPMC capsules are as simple to swallow as those made of gelatin.
n. Free of preservatives, allergens, starches, and gluten,
o. Printing can be done in a variety of ways, including axial, radial (spin), corrected axial, and double-printing. Logos can be packaged in appropriate materials, printed with acceptable inks, and given post-production treatments like lubrication spraying. Laser technology can be employed as a counterfeit prevention method,
p. can be easily colored using iron pigments, titanium dioxide, caramel, riboflavin, carmine, sodium copper chlorphyllin
q. It has received worldwide approval in terms of quick drug release and dissolution which were comparable to that of a gelatin capsule.

III. PRODUCTION CONDITIONS FOR EMPTY HPMC CAPSULE SHELLS [11-17]

A temperature-controlled solution of the shell material is used to dip mould pins before drying, placing, and stripping. This is the general manufacturing process for producing HPMC empty capsule shells. After the capsule's cap and body have been formed, the empty shell can be filled with a proper amount of a medicine and excipient mixture before being polished and sealed. Depending on the bioavailability need or the commercial objective, coating and banding may be done **[24]**.

In the following section, particular focus has been placed on intermediate steps used to manufacture HPMC capsule shells.

a. Gelation

Gelatin capsules are created through a process known as cold-set gelation, in which freezing causes inter-chain helices to become enthalpically stabilized and form individual chain segments that eventually form a three-dimensional network. In case of HPMC capsules, aqueous solution of methyl and hydroxyl propyl methylcellulose are known to gel upon heating i.e., heat-set gelation. These gels are entirely reversible since they solidify when heated but liquefy when cooled. The precipitation temperature, gelation temperature, and gel strength of these methylcellulose solutions were determined as a function of molecular weight, degree of methyl and hydroxypropyl substitution, concentration, and presence of additives.

The precipitation temperature of these polymer solutions decreases initially with increasing concentration until a critical concentration is reached above which the precipitation temperature is little affected by concentration changes. The incipient gelation temperature decreases linearly with concentration. The strength of these gels is time dependent, increases with increasing molecular weight, decreases with increasing hydroxypropyl substitution, and depends on the nature of additives.

b. **Gel promoter [18]**

The development of an appropriate gelling method during the fabrication of the empty HPMC capsule shell is necessary due to relatively reduced mechanical strength of the cellulose films. As of now, various natural polymers have been looked into as gelling agents. It has been demonstrated that carrageenan, a marine polysaccharide, specifically the kappa and iota types, causes HPMC to gel when present with potassium chloride at ambient temperature. This happens as a result of the carrageenan's ionotropic gelation in the presence of potassium ions, where the two substances serve as a network former, gelling agent, and gel promoter. With the use of this specific gelling technique, HPMC capsules can be produced using the same machinery as traditional gelatin capsules **[7, 10]**. This specific type of HPMC pill dissolves in stomach acid (pH 1.2). Similar results were obtained with gellan gum as the gelling agent and either ethylene diamine tetra acetic acid (EDTA) or sodium citrate as a gel promoter.

c. **Temperature regulation**

The temperature of the dipping pins or moulds used to create firm gelatin capsules should be 22 °C, and the gelatin solution should be maintained between 45 °C and 55 °C. Whereas in case of HPMC capsules production, the HPMC gelling solution must reach a minimum temperature of 70 °C in order to create a film. The temperature of the pins is controlled post-dip by using an induction heating system for the mould pins, to prevent the liquefaction of the films. In order to maintain the shape of the capsule, temperature should be kept constant till drying out of the films. It is important to note that the manufacture of HPMC capsule shells does not necessarily require moisture control.

d. Sealing and banding

Sealing is a process where the product becomes tamper-resistant, limits oxygen permeation through the shell, promotes the stability of the fill material, prevents leaking of the liquid fill material and also keeps any potent odors produced by the product inside the shell itself . Banding is a process applied to both gelatin and HPMC capsules where the junction between the two portions of the capsule is sealed using a sealing liquid and/or by placing a coating of layered solid material on the stated junction. . Banding of HPMC capsules is done by dissolving HPMC powder in binary solvent mixture of ethanol and water at room temperature, with > 50% w/w of ethanol. During this process usage of high ethanol content may speeds up drying, but the vapors obtained could lead to flammability and hazardous effects, as well. However, the performance of HPMC capsule on high speed filling machine can be improved by adding a gliding agent on the external surface of the capsule. But this process may lead to irregularity of the sealing/banding edge **[29]**. Ethanol-free banding can be done with HPMC-water solution along with small percentage of gelling agent which increases the band strength, reduces tendency for band shrinkage, minimizes air bubble formation and significantly reduces leakage rate.

The empty capsules are produced in accordance with GMP and ISO 9002 guidelines as a result, they have been granted FDA "Generally Recognized as Safe (GRAS)" certification. The resulting HPMC capsules demonstrated robust performance on high speed and semi-automatic filling machines with high output rates, low rejection rates (with less than 0.01% defects), and blister packaging equipments. They also had a flawless, shiny appearance, weight uniformity, and dimensional specifications that were found to be reproducible. All these factors speed up the development of dosage forms, making them more cost-effective for manufacture on a commercial scale. Additionally, liquid-filled modified HPMC capsules that were hermetically sealed as a single unit.

IV. FILL MATERIAL'S EFFECTS ON THE STABILITY OF THE HPMC CAPSULE SHELL [7, 19]

a. Hygroscopic fill materials can be used to fill HPMC capsules without compromising their mechanical stability or strength.
b. For a capsule-based DPI, an essential requirement is that the capsule should be punctured easily without being

broken into fragments which could have been inhaled. Since HPMC can withstand large variations in environmental humidity, it is resistant to breaking and produces a clean puncture without fragmentation when used in inhaler devices and does not shrink when stored in low humidity environments **[30]**.

c. The HPMC capsule for inhalation often has a slightly higher amount of moisture to have favorable drug delivery from device.

d. The amount of surface lubricant added to the mould pins during capsule fabrication, as well as the moisture level, determine the residual amount of drug in the capsule and inhaler device after actuation.

e. It is challenging to fill in liquids inside hard gelatin capsules, due to the potential for product-shell interactions. The liquid ingredient should be non-solvent for gelatin. But HPMC capsule can be filled with liquid fill material without compromising stability.

f. If the liquid state is below 35 °C, oils and lipids or medication solution in lipid phase can be easily packed in HPMC capsules. On the other hand, if the lipid phase is solid at 35 °C, they either become thixotropic mixtures or semi-solid matrices that are thermal softening mixes.

g. In HPMC capsules, semi-solid formulations up to 80 °C can be put.

h. HPMC capsules are now the preferred option for dry powder inhalers (DPI).

i. Triboelectrification (the accumulation o static charge) might enhance the affinity between dry API and the inside of the shell, resulting in insufficient dosage administration. When using HPMC capsules, this issue is less common.

j. Gelatin capsules turned brown when filled with ascorbic acid. This problem did not observed with HPMC capsules containing ascorbic acid, even when stored at 40 °C & 75% RH for 2 months.

k. When salicylic acid is employed as fill material in gelatin capsules at they get deteriorated. But when it is filled in HPMC capsules under identical conditions, a maximum of 2% deterioration was observed even when stored at 25 °C/ 60% RH for 18 months **[30]**.

l. After being kept at 45 °C for a month, gelatin and HPMC capsules containing a variety of liquid and semi-solid excipients (Propylene glycol, PEG 400, labrasol, triacetin, triethyl citrate, medium chain triglycerides, cottonseed oil, soybean oil, sesame oil, squalene, PEG 400-water-MCT emulsion, and gelucire 44/14) underwent visual inspection and a brittleness test. Out of all the excipients investigated, only propylene glycol softened both gelatin and HPMC capsules. Most liquid and semi-solid excipients were found to cause gelatin capsules to shatter where as HPMC capsules containing PEG 400 were deformed by Labrasol, All of the HPMC capsules except with PEG passed the brittleness test.

m. The HPMC capsule offers a very adaptable means for the formulator to broaden the options and address many of the issues now plaguing the pharmaceutical and nutraceutical sectors **[20]**.

V. QUALITY CONTROL TESTS FOR HPMC CAPSULE SHELL [7, 20]

It will be possible to confirm the use of HPMC as an alternative to gelatin as the capsule shell material only after analysing and contrasting the quality control parameters of the empty and filled HPMC capsules with hard gelatin capsules. The evaluation tests includes physico-mechanical factors like mechanical strength and gas permeability, physicochemical factors like the formaldehyde estimation, biopharmaceutical studies like *in vitro* and *in vivo* disintegration and dissolution tests, the esophageal sticking tendency test, animal studies, human bioavailability studies and finally the development of an *in vitro-in vivo* correlation and finally concluded by conducting stability studies on HPMC capsules under various temperature and humidity settings. Effects of all the parameters are discussed in following section.

a. Physical, mechanical, and chemical variables mechanical toughness [21]

The burst test or breaking-force test is employed for determining mechanical strength expressed as % brittleness which is a function of relative humidity for capsules stored under different conditions. Brittleness is directly related to quality, stability, consistency and resiliency of capsules and more so for liquid-filled hard capsules. During the test, no broken or otherwise compromised HPMC capsules were found at 2.5%-50% RH. With gelatin capsules, 100% of the samples were found to be brittle at 2.5% with no breakage at 50% RH.

b. Studies on gas permeability [7]

HPMC capsules give less protection against oxygen transmission (166 cc/m2/day) where as hard gelatin capsules have shown exceptional resistance to oxygen permeability (3.14 cc/m2/day), which may be due to looser structure of the HPMC film as observed in Scanning Electron Microscope (SEM) examinations of film cross-sections. In case of HPMC capsules if the formulation contains an anti-oxidant or that is packaged in a blister container with aluminium foil it can prevent the oxidation of sensitive APIs. When compared to gelatin capsules at all relative humidity percentages up to 40% at 25 °C, moisture absorption investigations using the dynamic vapor sorption method showed that HPMC capsules provided higher protection against moisture-induced deterioration of the fill material.

c. Test for formaldehyde exposure [22]

Different studies concluded formaldehyde exposure of Gelatin capsules with retard the drug release due to cross linking reaction induced by formaldehyde where as HPMC capsule shell is unchanged even after formaldehyde exposure **[7]**.

d. Test for in vitro disintegration [23, 24]

HPMC capsules without a gelling agent showed disintegration times of less than 10 min **[16]** as was seen with gelatin capsules in the disintegration test. But different studies has shown that HPMC capsules with carrageenan as gelling agent has delayed the capsule's initial burst in aqueous medium at body temperature. However, once the capsule has broken, a similar release profile to that of gelatin capsules was found which may be due to carrageenan's delayed hydration **[10]**.

i. The disintegration times of green tea extract loaded HPMC capsules, without gelling agent, were tested in acetate buffer and demineralised water and were found to be<30 min, satisfying the USP limits for herbal formulations. Cations in acetate buffer did not have any negative impact on HPMC shell material. However, gelatin capsules disintegrated comparatively faster.

ii. Disintegration time of spiranomycin loaded HPMC capsules in acidic medium (pH 1.2) was not altered, even after storage at 60 °C and 75% RH for 10 days. However, disintegration time was delayed with spiranomycin encapsulated in gelatin capsules.

iii. And these studies concluded that disintegration of HPMC capsules was not altered with media change or with change of API or by storing at 60 °C and 75% RH for 10 days but it slightly affected by the gelling agent used in the preparation of capsules.

e. Test for *in vitro* dissolution [7, 25, 26]

The dissolution studies of HPMC and gelatin capsules made-up of ibuprofen (BCS Class II) and acetaminophen (BCS Class III) were studied in different media and results were compared which states

i. In comparison to gelatin capsules, the release of ibuprofen from HPMC capsules was inadequate and extremely variable in neutral potassium phosphate buffer medium. This was explained by the presence of potassium ions (K+) in the dissolution medium.

ii. The drug release from both HPMC and gelatin capsules was complete and less variable in neutral tribasic sodium phosphate buffer (pH 7.2) medium. Acetaminophen released more slowly in neutral tribasic sodium phosphate buffer (pH 7.2) medium when sodium ions were present as opposed to potassium ions.

iii. Gelatin capsules break most easily. Since sodium ions do not bind as effectively as potassium ions, faster disruption is shown. The following discussion covers a number of variables that affect how HPMC capsules dissolve.

iv. The drug release profile of HPMC capsules generated without a gelling agent, however, was unaffected by the pH of the dissolution medium, the components of the medium, interactions with the shell material, or dietary components.

v. Due to carrageenan's solubility at pH-4, HPMC capsules were produced with carrageenan as a gelling agent dissolved in gastric fluid (pH 1.2), whether eaten before or after meals **[21]**.

vi. During the dissolution investigation from both types of HPMC capsules in Fed State Simulated Intestinal Fluid (FeSSIF), the effect of food interaction was obvious. Giving HPMC capsules on an empty stomach is advised The addition of digestive enzymes to the dissolution medium did not change the drug release profile for either gelatin or HPMC capsules in mixed phosphate buffer (pH 6.8).

vii. In a research it was concluded that in order to ensure therapeutic effectiveness, gelatin capsules are best taken with warm beverages, while HPMC capsules can be taken with either cold or warm beverages **[29]**.

viii. For HPMC capsules of sizes 0 and 3, statistically significant changes in dissolution times were seen **[28]**. Another investigation found that HPMC capsules of various sizes that had been made without a gelling agent had the same drug release profile **[16]**.

f. A propensity for esophageal sticking [27, 28]

Given that HPMC is a bio adhesive substance, an increase in the esophageal residence period before reaching the stomach is anticipated. When tested on healthy male volunteers, neither HPMC nor gelatin capsules showed any protracted esophageal hold up or sticking propensity.

However, it was advised that solid dose forms be consumed in an upright position with at least 50 ml of water to minimize esophageal entrapment.

g. Test for *in vivo* dissolution and disintegration [28]

Studies utilizing varying viscosity grades of HPMC powder in prolonged release radio-labeled formulations in healthy human volunteers indicated that HPMC capsules dissolved in 9 minutes as opposed to 7 minutes for gelatin capsules. As a result, it has been found that the gradual disintegration or dissolution of HPMC capsules in water or phosphate buffer (pH 6.8 or 7.2) in a laboratory setting has no adverse effects on the disintegration or dissolution of the capsules in living organisms. As a result, HPMC capsules might be thought of as an excellent substitute for gelatin capsules.

h. Study on bioavailability [29]

Based on the analysis of plasma data from male dogs that had received single dosage capsules when fasting or fed, it was shown that HPMC capsules produced a rapid *tmax* for immediate release formulations, proving that the absorption was not slowed down by the breakdown of the capsule shell. Studies on bioavailability in healthy human volunteers showed that the HPMC capsule shell quickly disintegrates, with a median *tmax* of roughly 1 hour in the fasting condition. As a result, HPMC capsules give humans a fast *in vivo* plasma profile.

i. *In vitro- In vivo* correlation [7, 28]

Due to the reported in vitro interaction between the medium and the HPMC capsule gelling systems, which is not apparent in *in vivo* investigations on animals or human volunteers, HPMC capsules may show minimal correlation between the in vitro dissolution/disintegration and the in vivo performance. Dissolution/disintegration testing requirements should be different from those for hard gelatin capsules in order to achieve better correlation. Two-tier dissolving tests should be used for hard gelatin capsules, and dissolution studies from HPMC capsules should also use comparable changes.

j. Stability Studies [7]

200 HPMC capsules were placed in glass bottles and cooked for 24 hours in an oven at various temperatures (up to 90 °C). Before opening the glass containers, the capsules were visually assessed for mechanical strength and disintegration-dissolution performance. The glass bottles were maintained at room temperature for at least 5 hours. Although deformation occurred at 70 °C, no visible changes in the appearance of HPMC capsules held at 40 °C could be seen. Even at 90 °C, mechanical strength and disintegration-dissolution performance were unaltered.

However, when changes were reflected in all the parameters examined, it was discovered that 60 °C was the highest temperature that gelatin capsules could tolerate **[7]**. While tested under the same circumstances and also when subjected to temperatures ranging from 4 °C to -18 °C, similar results were achieved in a different investigation. Studies on long-term stability at 40 °C and 75% relative humidity (RH) for 6 months, as well as at 25 °C and 65% RH or 30 °C and 70% RH for 2 years did not show any changes in the features of disintegration and dissolution.

VI. ADVANTAGES OF HPMC CAPSULES [29]

- They are the best alternative to gelatin capsules
- They are best suitable for vegetarians, diabetics& patients with restricted diet
- They are organic, vegan, herbal, all natural, non-allergenic, soy or gluten free
- They have Improved Brittleness
- They have good chemical stability resulting improved Dissolution profile
- Suitable at low Humid Condition
- Pharmaceutical-grade quality
- Available in a wide range of colors
- Available in all sizes
- Approved by different Regulatory Authorities
- Compatible in high-speed filing machines
- Suitable for Drug powder inhaler (DPI) product

VII. DISADVANTAGES [29]

- Occasionally they may have cracked caps, dimpled bodies, and incorrectly closed caps, HPMC capsules were unsatisfactory
- Because HPMC capsule walls are substantially more fragile than gelatin shells, handling should be done with greater caution
- High cost of production
- Processing issues arise from HPMC shells
- Lower tensile strength and reduced resistance to indentation compared to gelatin shells.

VIII. APPLICATIONS 14, 16,17, 18, 20, 30

HPMC capsules have wide applications in Pharmaceutical like

1. Novel drug delivery system:
2. In Controlled release drug delivery system:
3. Oro mucosal drug delivery systems:
4. HPMC capsules is the standard choice for dry powder inhalers **[2, 6]**.
5. As Enteric coated Capsules:

6. Novel approach to sustained release drug delivery:
7. For Preparation of hard capsules:
8. HPMC capsules for nutraceuticals
9. HPMC capsules for probiotics
10. Targeted delivery

IX. CONCLUSION

Gelatin is the most frequently used material for capsule shells. However it has a number of disadvantages. The primary drawbacks of gelatin capsules, such as the phenomenon of cross-linking, variable mechanical strength under altered processing or storage temperature and relative humidity, preferential compatibility with only certain types of fill materials and excipients, and lack of versatility, have been successfully overcome by hydroxy propyl methyl cellulose, a semi-synthetic alternative with superior physicochemical, pharmaceutical, and biopharmaceutical properties. Studies conducted by numerous manufacturing businesses and research labs have shown that HPMC capsules are superior than hard gelatin capsules in terms of mechanical strength and compatibility with a variety of pharmaceuticals and excipients with reactive functional groups and variable degrees of hygroscopicity. High temperatures exhibit better short-term stability, and flexibility is preserved even at low relative humidity levels. Because of their botanical origin, HPMC tablets have greater commercial potential because more patients accept them. To ensure the formation of a high level of in vitro-in vivo correlation, the processing processes for HPMC capsules must be enhanced in terms of their machinability, and required modifications to the dissolving research procedure must be made.

CONFLICT OF INTERESTS

Nil

REFERENCES

[1] Rampurna P Gullapalli, Carolyn L Mazzitelli, Gelatin and Non-Gelatin Capsule Dosage Forms, Journal of Pharmaceutical Sciences, 106(6), 2017, 1453-1465.

[2] George A Digenis, Thomas B .Gold, Vinod P Shah, Cross-Linking of Gelatin Capsules and Its Relevance to Their in Vitro-in Vivo Performance, Journal of Pharmaceutical Sciences, 83(7), 1994, 915-921.

[3] Gilbert S. Banker, Juergen Siepmann, Modern Pharmaceutics. 4, Boca Raton, 2002, CRC Press; 2002, 511-575.

[4] Sowmya C, Surya Prakash Reddy C, Capsules And It's Technology: An Overview, International Journal of Pharmaceutics and Drug Analysis, 2(9), 2014, Page:727-733.

[5] Margareth R. C. Marques, Enzymes in the Dissolution Testing of Gelatin Capsules, AAPS PharmSci Tech, 15(6), 2014, 1410–1416.

[6] Rakesh Hota, Simanchal Panda1, Sruti Ranjan Mishra, A Review On Vegetarian Capsules, World Journal of Pharmaceutical Research, 7(9), 2018, 316-323.

[7] Sutapa Biswas Majee, Dhruti Avlani, Gopa Roy Biswas, HPMC as Capsule Shell Material: Physicochemical, Pharmaceutical And Biopharmaceutical Properties, International Journal of Pharmacy and Pharmaceutical Sciences, 9(10), 2017, 1-6.

[8] Rahul Khiste, Nilkanth Bhapkar, Nilesh Kulkarni, A Review on Applications of Hydroxy Propyl Methyl Cellulose and Natural polymers for the development of modified release drug delivery systems, Research Journal of Pharmacy and Technology, 14(2), 2021, 1163-1170,

[9] Majee S B, Avlani D, Biswas G R, "HPMC as Capsule Shell Material: Physicochemical, Pharmaceutical and Biopharmaceutical Properties". Int J Pharmacy and Pharmaceutical Sciences, 9(10), 2017, 1–12.

[10] Annamadevi G. S, V. T. Iswarya, Coprocessed excipients: Uniqure Approch in Pharmaceutical Industry, High Technology Letters, 27(11), 2021, 621-635.

[11] Grosswald R R., Anderson J B, Andrew CS, Method for the manufacture of pharmaceutical cellulose capsules. US Patent No. 5, 1997. 698,155.

[12] Grosswald R R., Anderson J B, Andrew CS, Apparatus for the manufacture of pharmaceutical cellulose capsules. US Patent No. 5, 1998, 750,157.

[13] Grosswald R R., Anderson J B, Andrew CS, Method for the manufacture of pharmaceutical cellulose capsules. US Patent No. 5, 1998, 756,036.

[14] Grosswald R R., Anderson J B, Andrew CS, Method for the manufacture of pharmaceutical cellulose capsules. US Patent No. 6, 2002. 337,045.

[15] Yamamoto T, Abe K. Matsuura S. Hard capsule for pharmaceutical drugs and method for producing the same. US Patent No. 5, 1993, 264,223.

[16] Yamamoto T, Abe K. Matsuura S., Hard capsule for pharmaceutical drugs and method for producing the same. US Patent No. 5, 1995, 431,917.

[17] Tuleu C, Khela M K, Evans D F, Jones B E, Nagata S, Basit AW, A Scintigraphic Investigation of The Disintegration Behaviour of Capsules in Fasting Subjects: A Comparison of Hypromellose Capsules Containing Carrageenan As A Gelling Agent and Standard Gelatin Capsules. European Journal of Pharmaceutical Sciences, 30 (3-4), 2007, 251- 55.

[18] Siepmann, J., & Peppas, N. A. (2012). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced drug delivery reviews, 64, 163-174.

[19] Missaghi S, Fassihi R, Evaluation and comparison of physicomechanical characteristics of gelatin and hypromellose capsules. Drug Development and Industrial Pharmacy, 32 (7), 2006, 829-838.

[20] Ku M S, Li W, Dulina W, Donahue F, Cade D, Benameur H, Hutchisonc K, Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps Plus, Quali-V and gelatin capsules, Int J Pharm, 386, 2010, 30-41.

[21] Luigi Fappiano, Fabiana Carriera, Alessia Iannone, Ivan Notardonato, and Pasquale Avino , A Review on Recent Sensing Methods for Determining Formaldehyde in Agri-Food Chain: A Comparison with the Conventional Analytical Approaches, Foods. 2022, 11(9): 1351-1357.

[22] Cole E T, Scott R A, Connor A L, Wilding I R, Petereit H U, Schminke C, Beckert T. Cadé D. Enteric coated HPMC capsules designed to achieve intestinal targeting. International Journal of Pharmaceutics, 2002, 231 (1), 83-95.

[23] Honkanen, Seppa H, Eerikäinen S, Tuominen R, Marvola M, Bioavailability of ibuprofen from orally and rectally administered hydroxypropyl methylcellulose capsules compared to corresponding gelatine capsules. STP Pharma Sciences, 2001, 11(2), 181-185. 2001

[24] Chiwele, Jones B E, Podczeck F, The shell dissolution of various empty hard capsules. Chemical and Pharmacutical Bulletin, 2000, 48 (7), 951-956.

[25] Tochio S, Nagata S, Yamashita S,

The influence of the composition of test fluids on dissolution from HPMC capsules. AAPS Pharm Sci, 2002, 4(S1), W4340.

[26] Batchelor H. Bio adhesive dosage forms for esophageal drug delivery. Pharmceutical Research, 2005, 22, 175-181.

[27] Moawia M Al-Tabakha, HPMC capsules: current status and future prospects, Journal of Pharmacy and Pharmaceutical Sciences, 2010, 13 (3):428-442.

[28] Mašková E., Kubová K., Raimi-Abraham B. T, Vllasaliu D., Vohlídalová E., Turánek J, Mašek, J, Hypromellose–A traditional pharmaceutical excipient with modern applications in oral and oromucosal drug delivery. Journal of Controlled Release, 2020, 324, 695-727.

[29] Hadi A., Rao N G, Rao A S, Shiva G, Akram J, Impact of capsules as a carrier for multiple unit drug delivery and the importance of HPMC capsules, Research Journal of Pharmacy and Technology, (2013, 6(1), 34-43.

[30] Maribel Jimenez, Enrique Flores, Luz A. Pascual-Pineda, Cesar I. Beristain, Effect of Water Activity on the Stability of Lactobacillus paracasei Capsules, Food Science and Technology, 2015, 60 (1), 346–35.